EXHIBIT A

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

In Re Flint Water Cases,

No.: 5:16-cv-10444-JEL-MKM
(consolidated)

Hon. Judith E. Levy

Magistrate Mona K. Majzoub

I, William G. Bithoney, MD, FAAP, individually, under penalty of perjury, hereby affirm that the foregoing is true and correct:

1. I currently reside in Fayetteville, GA.

2. I am a M.D. from the Yale University School of Medicine with a Doctoral Dissertation in The Neuropsychiatric Complications of Viral Encephalitis. My Postdoctoral training has been in Pediatrics from the Yale University School of Medicine. I have dedicated my career to helping children, especially those exposure to lead poisoning. A true and correct copy of my CV is attached hereto.

3. I have reviewed the various objections focused on the bone lead testing program undertaken in Flint, Michigan where it is alleged that such testing is unsafe. I submit this Declaration in opposition to these statements and provide the following opinions to a reasonable degree of medical certainty. To be clear, bone lead testing

as utilized in the Flint Water Litigation is safe and a valuable tool for the purposes of establishing lead exposure.

4. I have worked in the field of pediatrics for over thirty-five (35) years and have held various academic and consulting positions pertaining to pediatrics. My experience is extensive, including:

- Associate in Medicine at Children's Hospital, Boston, from 1985 to 1991, and Senior Associate in Medicine at Children's Hospital, Boston, from 1992 to 1996.
- Senior Associate in Medicine is the highest clinical appointment available at Harvard Medical School
- Physician-in-Chief at St. Joseph's Children's, Paterson, NJ, from 1999 to 2002.
- Chief Medical Officer. Mercy Health System Philadelphia Pennsylvania from 2002 to 2005
- Vice Dean at the New York Medical College, Valhalla, NY, from 2005 to 2007.
- Instructor in Pediatrics at Harvard Medical School from 1979 to 1986.
- Assistant Professor in Pediatrics at Harvard Medical School from 1986 to 1996.

- Associate Professor in Pediatrics at Harvard Medical School from 1996 to 1997
- Professor of Pediatrics at the State University of New York (SUNY)1997 to 2005
- Professor of Pediatrics at New York Medical College, Valhalla, NY, from 2005 to present. (Inactive)
- CEO at Bithoney and Associates Accountable Care Consulting Group from 2012 to present.

5. I have served as Chief Medical Officer ("CMO") for a number of large health systems such as Mercy Hospital, Philadelphia, PA, Mercy Health System, Conshohocken, PA, and Sisters of Providence Health Systems of MA and CT. I also specialize in efficient clinic and hospital management and have developed self-sustaining models for performance and quality improvement, management, and research strategies.

6. Additionally, I have extensively researched Lead Poisoning and its effects on children's health. Some of my research articles and presentations pertaining to lead poisoning in children include:

- Bithoney WG, Elevated Lead (Pb) Levels in Undernourished Children. Pediatrics 1986 Nov.; 78:5:891-895.

- Bithoney WG, Ryan A., Vandeven A. Elevated Lead (Pb) Levels in Abused Children. Journal of Pediatrics 1993; 122:719-720.
- Bithoney WG, Elevated Lead Levels in "Non-Organic" Failure to Thrive (FTT): A Potential Organic Contributant. Presented at the Ambulatory Pediatric Association Meeting, San Francisco, April 30, 1984.
- Serving the Underserved: Educational Guidelines for Pediatric Trainees, Editor and Author Lead Poisoning Guideline, 1992. Publication sponsored and funded by the American Academy of Pediatrics and the Ambulatory Pediatric Association.

7. While I am not a radiology specialist, I familiar with and aware of the portable X-Ray fluorescence ("XRF") scanning program for bone testing of lead. In my work as a chief medical officer of health systems I was, for many years in charge, along with colleagues in radiology, of the safety of patients exposed to radiation in our radiology and radiation oncology divisions. Further, I have studied the specifics of the device used in bone lead testing in this matter. I have also studied the implementation of the program and have read the research pertaining to this method off XRF scanning for bone testing for lead in children.

8. It is important to understand the radiation exposure associated with the XRF test employed in evaluating the children of Flint. Using a portable XRF device

to test for lead exposes the body to an extremely low dose of radiation. Compared to exposure from x-ray machines, CT scans, and MRI scans, the exposure to radiation from the XRF device is negligible and poses negligible risk to humans. To be exact, exposure to radiation from an XRF scan for bone testing of lead is measured at a dose of ~3.4 micro sieverts. In comparison, exposure to radiation from a standard chest x-ray is 100 micro sievert.[1] Please see **Exhibit A**. It is my opinion that there is negligible risk of long-term or short-term effects from exposure to the above-mentioned amount of radiation, which is negligible, in either adults or children.

9. According to the International Atomic Energy Agency (IAEA) homepage statement on Radiation in Everyday Life: "naturally occurring radioactive materials are present in the Earth's crust, the floors and walls of our homes, schools and offices and in the food we eat and drink. There are radioactive gases in the air we breathe. Our own bodies-muscles, bones and tissue-contain naturally occurring radioactive elements and emit radiation." In addition, according to the IAEA we are constantly being bombarded by cosmic radiation entering the Earth's atmosphere from outer space. Due to these varying sources of radiation all humans are exposed to approximately 2400 micro-sievert's (2.4 miliSvs) of radiation per annum. We receive approximately 6.5 micro-sievert's per day of radiation from ambient

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[1] Specht A.J., Zhang X., Goodman B.D., Nie L.H., et al., A Dosimetry Study of Portable X-Ray Fluorescence In Vivo Metal Measurements, www.health-physics.com, May 2019, Vol. 116, Number 5

conditions (living and breathing). As noted, children of Flint undergoing XRF evaluation for lead level determination are exposed to approximately 3.4 micro-sievert's of additional radiation from the XRF scan for bone lead. Thus, the additional radiation exposure caused by the XRF bone lead test used to evaluate lead levels in these children is the equivalent of the children simply living and breathing for 12 hours. The radiation dose these children receive is less than what they would receive simply by taking a typical airplane ride, which exposes us to approximately 0.003 millisieverts per hour, or about 3.0 micro-sievert's per hour, approximately the same amount of exposure to radiation a child receives during the XRF bone lead test.[2] The potential damage of this radiation dosage is in my opinion negligible when considering radiation risk of the procedure. (Source: IAEA.org homepage "Radiation in Everyday Life and the United States Nuclear Regulatory Commission, NRC.gov home page "Radiation All Around US".

10. The American College of Obstetricians and Gynecologists ("ACOG") has recommended using certain diagnostic imaging procedures during pregnancy[3]. Please see **Exhibit B**. They specifically say, "Radiation exposure through radiography, computed tomography (CT) scan, or nuclear medicine imaging

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[2] https://theconversation.com/air-travel-exposes-you-to-radiation-how-much-health-risk-comes-with-it-78790

[3] Copel J. MD, El-Sayed Y., MD, Heine R.P., MD, and Wharton K.R., MD, ACOG Committee Opinion: Guidelines For Diagnostic Imaging During Pregnancy And Lactation, Obstetrics & Gynecology, Vol. 130, No. 4, October 2017

techniques is at a dose much lower than the exposure associated with fetal harm. If these techniques are necessary in addition to ultrasound or MRI or are more readily available for the diagnosis in question, they should not be withheld from a pregnant patient.".[4]

11. Further, it is my opinion that the XRF test poses negligible risk to a fetus because the radiation exposure is much less than that of exposure from CT scans, ultrasounds, or MRIs, which is said to be safe for pregnant women to undergo by the ACOG. Further, the XRF scan for bone testing of lead program in Flint is conducted by targeting the superficial part of the tibia, or the shinbone, which is distant from the fetus and other vital organs. Consequently, the fetus is being exposed to virtually zero radiation from the XRF scanning test.

12. Boston Children's Hospital's Nuclear Medicine and Molecular Imaging Program for bone scan tests on children uses a non-invasive imaging technique that employs a radioactive substance to visualize the bones.[5] Please see **Exhibit C**. The program ensures that children undergoing the test are exposed to very small doses of radiation and further explains that "nuclear medicine has been used on babies and children for more than 40 years with no known adverse effects from the low doses employed," and "it is safe to be in the room with your child the

[4] *Id.*

[5] https://www.childrenshospital.org/conditions-and-treatments/treatments/bone-scan

entire time, even if you are pregnant or nursing."[6] Similarly, the XRF scan for bone testing for lead in Flint exposes the child to a negligible amount of radiation and produces almost no scatter, ensuring that a pregnant mother in the room with her child is safe, as is her fetus.

13. The Center for Disease Control ("CDC") also states that exposures to radiation from diagnostic medical exams are unlikely to cause health effects for a fetus within regulatory limits.[7] Please see **Exhibit D**. Diagnostic medical exams are permitted, which expose patients to radiation at a dose considerably higher than the dose from the XRF scan used in Flint.

14. Based on the above mentioned research, my education and experience in pediatric medicine and health, I am confident in the XRF Bone Lead Testing Program as an accurate and safe means of measuring long-term lead exposure.

Dated: 5/24/21

Signature: William C. Bithoney MD, FAAP

Name: William Bithoney

[6] *Id*

[7] Radiation and Pregnancy: Information for Clinicians, Center for Disease Control and National Center for Environmental Health Agency for Toxic Substances and Disease Registry, April 29, 2019

Exhibit A

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Paper

A DOSIMETRY STUDY OF PORTABLE X-RAY FLUORESCENCE IN VIVO METAL MEASUREMENTS

Aaron J. Specht,[1] Xinxin Zhang,[2] Benjamin D. Goodman,[3] Ed Maher,[1] Marc G. Weisskopf,[1] and Linda H. Nie[2]

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Abstract—**Portable x-ray fluorescence devices have grown in popularity for possible metal exposure assessment using in vivo measurements of bone and toenail. These measurements are accompanied by a small radiation dose, which is typically assessed by radiation safety committees to be minimal. However, an understanding of precise dose under different instrument conditions is still needed. This study set out to do a thorough investigation of the exact dose measurements using optically stimulated dosimeters, thermoluminescent dosimeters, and simulation with a Monte Carlo N-Particle transport code to assess the skin and total-body effective dose typical of portable x-ray fluorescence devices. We showed normal linear relationships between measurement time, x-ray tube current, and radiation dose with the device, and we showed a second order polynomial relationship with increasing voltage and radiation dose. Dose was quantified using thermoluminescent dosimeters, optically stimulated dosimeters, and simulations, which gave similar dose estimations. Skin dose for a standard 50-kV, 40-μA measurement for bone and toenail in vivo was 48.5 and 28.7 mSv, respectively, according to simulation results. Total-body effective dose was shown as 3.4 and 2.0 μSv for in vivo bone and toenail measurements, respectively, for adults using the portable x-ray fluorescence device.**

Health Phys. 116(5):590–598; 2019

Key words: dose assessment; exposure, radiation; metal, trace; radiation effects

INTRODUCTION

PORTABLE X-RAY fluorescence (XRF) devices are being used more frequently for in vivo measurements to assess metal exposures in populations. The risks associated with the radiation exposure from these low-energy x-ray tubes are minimal, but since they are used in population studies, a more thorough review of the radiation exposure would be appropriate to fully consider the radiation exposures associated with the use of portable x-ray fluorescence devices.

Metal exposure assessment has been performed for decades using x-ray fluorescence. Previous devices for x-ray fluorescence measurements used radionuclides as a source to stimulate the characteristic x-ray emissions (Chettle et al. 1991). In particular, the ^{109}Cd radionuclide K-shell XRF device for lead measurement had well-characterized radiation dose, which was summarized in a previous study (Nie et al. 2007). The radiation dose associated with portable XRF measurements has not been characterized as accurately and thoroughly. Only one previous study has explored the radiation dose with measurements using thermoluminescent dosimeters (Nie et al. 2011). However, it was quickly found after optimization of the device that the x-ray tube current used for this measurement was not optimal, and changes in x-ray tube settings were proposed for future studies, and further changes are likely in the future to optimize for different metal or tissue measurements (Specht et al. 2014).

Portable XRF presents a unique problem since the device uses a modifiable source, which can be used on different tissues to measure different biomarkers of exposure. Changes to the source or tissue examined would result in changes to the radiation dose and radiosensitive organs in the measurement. In this study, we measured radiation dose from a portable XRF and identified the changes in dose with different x-ray tube voltage, current, and filtration when doing bone lead and toenail metal measurements.

MATERIALS AND METHODS

Portable XRF device

We used a Thermo Fisher XL3t GOLDD+ portable XRF device for this study (Thermo Fisher Inc., Billerica, Massachusetts, US). The device is typically used commercially for mining and soil measurements but has been investigated for use in metal exposure assessment in vivo. This study focuses on in vivo uses and the associated radiation dose. This same x-ray system has been used in previous studies measuring bone in vivo for strontium and lead, and

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The authors declare no conflicts of interest.

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for measuring toenails in vivo for mercury and manganese (Specht et al. 2014, 2016, 2017a and b; Zhang et al. 2017). For this study, we used variable voltage, current, and filters from the device, which we note in the results for our measurements. The maximum power output of the x-ray tube was 2 W.

Standard phantoms

Soft tissue and bone equivalent phantoms were used in this study to determine the dose for in vivo bone measurements. Lucite (Lucite International UK, Ltd., Southampton, UK) plate phantoms were used to simulate soft tissue over bone by placing the Lucite under the flat surface of the bone phantoms in increments of 1 mm up to 5 mm of Lucite thickness. These Lucite plates were found to be an acceptable phantom for soft tissue in our previous study (Specht et al. 2014). Cylindrical phantoms with a flat base for measurements were made of plaster of paris and were used to simulate bone. These measurements were made from the flat base of the phantom.

Toenail phantoms were made to test in vivo measurements of toenail metals. Standard phantoms for toenails were made using epoxy resin with added salt to standardize the attenuation coefficients, similar to prior work (Roy et al. 2010; Zhang et al. 2017). For the dose assessment we used toenail with 0.6 and 1.3 mm to determine the influence of toenail thickness on the radiation dose.

Optically stimulated luminescence dosimetry system

For this study we used a Landauer InLight MicroStar Optically Stimulated Luminescence Dosimeter (OSLD) reader (Landauer, Glenwood, Illinois, US). This system has been used in studies of similar surface dose measurements in clinical practice (Yusof et al. 2015). The system was calibrated using standard OSLDs obtained from Landauer. Two calibrations were completed, one for low-dose response (3 OSLDs between 0.10 to 10 mGy) and one for high-dose response (3 OSLDs between 0.01 to 15 Gy). The measurements of calibration OSLDs were made nine times to ensure accuracy, and it was found that there was <2% change between readings, which fit the qualifications for clinical use of OSLD measurements according to TG-191 American Association of Physicists in Medicine (AAPM) recommendations (AAPM 2017). The OSLDs used for dose measurements were found to be accurate within 10% with repeated measures of the same x-ray settings, which is primarily due to a higher background dose present in many of the OSLDs. Error from these measurements are represented in the figures as a measure of the error identified in our repeatability tests during measurements. We used these measurements to get a sense of the characteristic relationships between the portable XRF radiation dose and different situations, and we did not expect a calibration of these OSLDs to produce quantified results within clinical-level accuracy from this study.

We measured the radiation dose from a variety of settings and setups of phantoms. We first used a number of different geometries with the OSLDs in order to find the maximal dose. We measured the dose using x-ray tube settings 50 kV, 40 μA, and an iron and silver filter changing the time from 0.5, 1, 2, 3, and 4 min. We also did tests changing the current from 40 μA to 30, 20, and 10 μA, while keeping the other settings the same; then doing the other iterations, changing the voltage to 40 kV and changing the current from 50 μA to 40, 30, 20, and 10 μA with filtration and time constant. We did tests using aluminum and titanium, molybdenum and iron, and iron and silver filtration, which could prove to be useful for certain in vivo measurements.

Finally, we did dose measurements using 50 kV, 40 μA, and silver and iron filtration for bone and skin measurements. We used 0, 1, 3, and 5 mm of skin thickness to induce scatter. Then we used bare bone with no skin phantoms, 3-mm skin with bone, and 5-mm skin with bone. We attempted to estimate surface bone dose by placing the OSLDs between the skin and bone phantom at 1, 2, 3, and 5 mm of skin. Lastly, we did tests of entrance and exit dose to toenail phantoms with thicknesses of 0.6 and 1.3 mm using both 50-kV, 40-μA and 40-kV, 50-μA x-ray tube settings with silver and iron filtration.

Thermoluminescent dosimeters

Thermoluminescent dosimeters (TLDs) were used in this study for further validation of the dose readings. TLD 700 chips were used in this study, since the dose associated with XRF is purely from photons. The TLDs were read using a Harshaw TLD 4000 reader (Harshaw Partnership, Solon, Ohio, US). The TLDs were calibrated against known exposures from a gamma irradiator at Purdue University. A Gammacell 220 (Nordion International Inc., Ottawa, Canada) containing a ^{60}Co radionuclide source with known exposure rates. Each TLD used in this study was separately irradiated for doses of 0, 25, 50, 75, 125, 250, 500, and 1,000 mR (the units in which the source is calibrated for exposure), which were each measured three times to ensure the accuracy of the TLDs. The combined calibration curves of the TLDs produced a line with a correlation R^2 of 0.995, which gave us confidence in the quantification and accuracy of results obtained using these TLDs.

We first used a number of different geometries for measurement to find the maximal dose for the TLD measurements. The portable XRF comes standard with a camera, which can identify items placed in the field of view of the x-ray tube, which we used for verification of dosimeter placement consistency. We measured these dosimeters with x-ray tube settings of 50 kV, 40 μA with an iron and silver filter for 3 min under soft tissue and bone phantoms, and 40 kV, 50 μA with an iron and silver filter for 3 min under toenail, Lucite soft tissue phantoms, and bone phantoms.

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Finally, we used a grid pattern of four TLD chips to average over and better recreate our normalized skin area of 1 cm^2 (this approach approximated an area of ~0.8 cm^2).

Monte Carlo simulations

We used the Monte Carlo simulation program, Monte Carlo N-Particle (MCNP) transport code, in our study, which was developed by Los Alamos National Lab and distributed by the Radiation Safety Information Computational Center. This software has recently been updated to more accurately depict interactions at lower energies, using its default database for interaction cross sections. This includes Doppler broadening effects and all interactions observed in XRF. In a previous study, we validated the use of this simulation to accurately simulate the output from the x-ray tube of the exact portable XRF used in this study (Specht et al. 2017b). There was less than 9% difference between simulated and experimental spectral from that study. MCNP gives us the ability to set unique materials, densities, geometries, and sources in order to reproduce an experimental setup and, in the case of this study, to reproduce the dose of in vivo measurements. Previous studies have similarly used MCNP to estimate dose to patients in clinical settings (Yoriyaz et al. 2001). We used the same x-ray tube simulation as our previous study but added in skin, bone, or toenail based on the specifications for our study. We did simulations to reproduce the in vivo bone measurements and give estimates for bone and skin dose. We also did simulations of toenail in vivo measurements to look at skin dose below the toenail. The bone and skin composition and densities were taken from International Commission on Radiation Units and Measurements (ICRU) Report 44 (ICRU 1989), and the toenail composition was taken from Rutherford and Hawk (1907). The simulation included a 40-cm-long leg, which was used in full for energy deposition measurements in the total-body effective dose calculations. For skin dose, only a 1-cm^2 voxel of the skin in the maximal area of exposure was used for dose measurements. In the calculations of dose, we used the number of particles that would have been used in the x-ray tube based on the amperage and a time of 3 min, which should make the measurements equal to those with TLDs and OSLDs with 3-min exposures.

Total-body effective dose calculations

We calculated total-body effective dose for the bone measurement using the simulation to get total skin and total-surface bone dose from the simulated 40-cm-long leg. For the toenail measurements, we assumed the same area of exposure except with the added attenuation of toenail. The dose from the bone was assumed to be all-surface dose, since the penetration depth of x rays from the portable XRF would only be ~0.5 mm into the bone. We used a simulation with skin (skin thickness 5 mm) and bone tissue 40 cm in length (bone radius 1.25 cm) to ensure we captured the full dose of any scattering that occurred. We approximated the total-body bone surface using different values for 5-y-old, 10-y-old, and adult females and males. From Specker et al. (2001), 5-y-old male and female bone area was taken to be 950 and 935 cm^2, respectively. For adult males and females, we used a 2013 Centers for Disease Control (CDC) report on total-body bone area with values 1,385 and 1,399 cm^2 for 10-y-olds and 2,272 and 1,918 cm^2 for adults (Looker et al. 2013). We assumed the density of bone was 1.7, 1.75, and 1.8 g cm^{-3} for 5-y-old, 10-y-old, and adult, respectively, as taken from the table on page 37 of International Commission on Radiological Protection (ICRP) 70 (ICRP 1995). For skin areas we used 0.78, 1.12, and 1.90 m^2 for 5-y-old, 10-y-old, and adult, respectively (ICRP 2002). We also included a comparison of total-body effective dose with different tissue thickness values of 1, 3, and 5 mm.

RESULTS

OSLD results

Fig. 1 shows the linear dose relationship with measurement times using 50 kV, 40 μA, and iron and silver filtration.

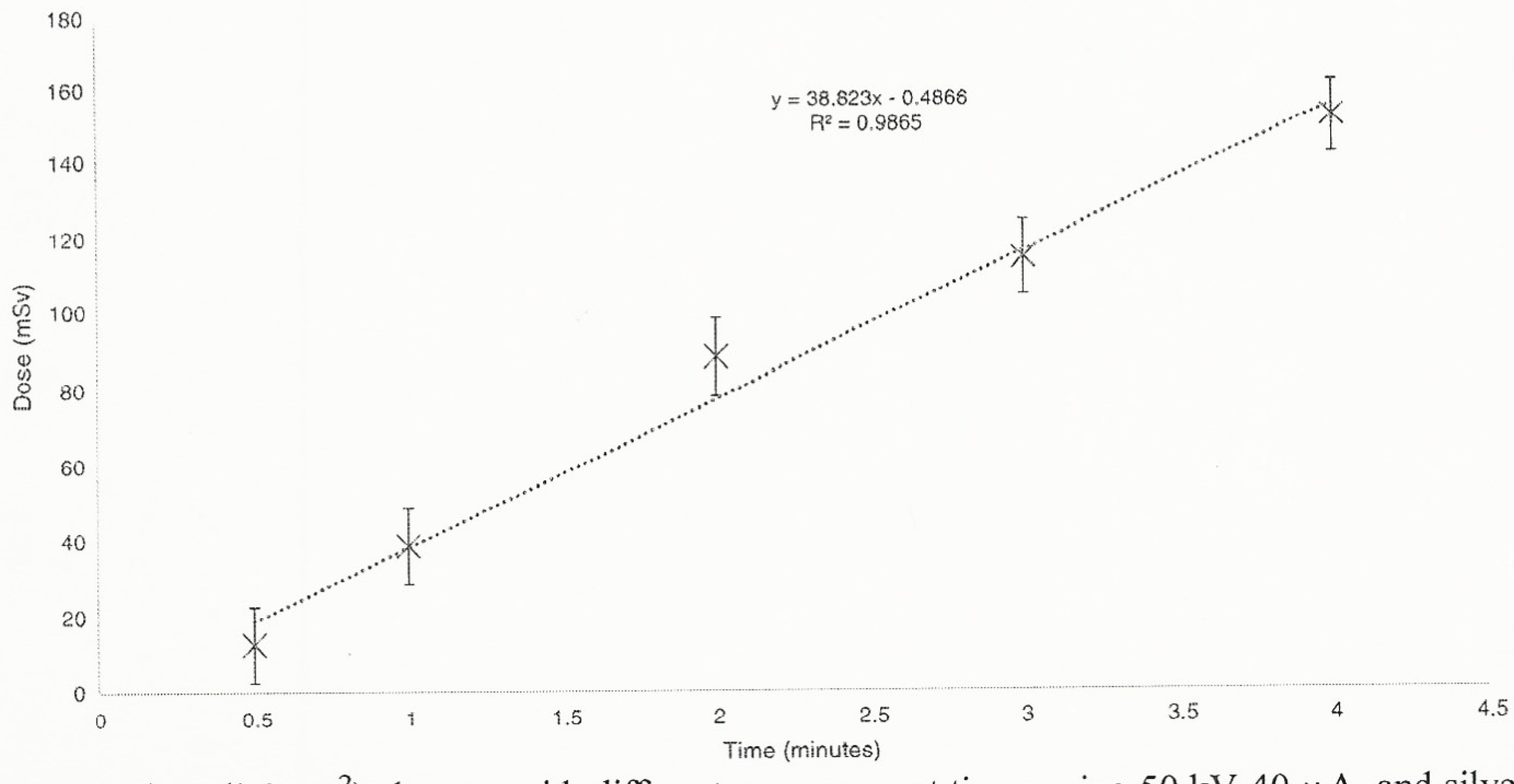

Fig. 1. Radiation entrance skin dose (0.2 cm^2) changes with different measurement times using 50 kV, 40 μA, and silver and iron filtration.

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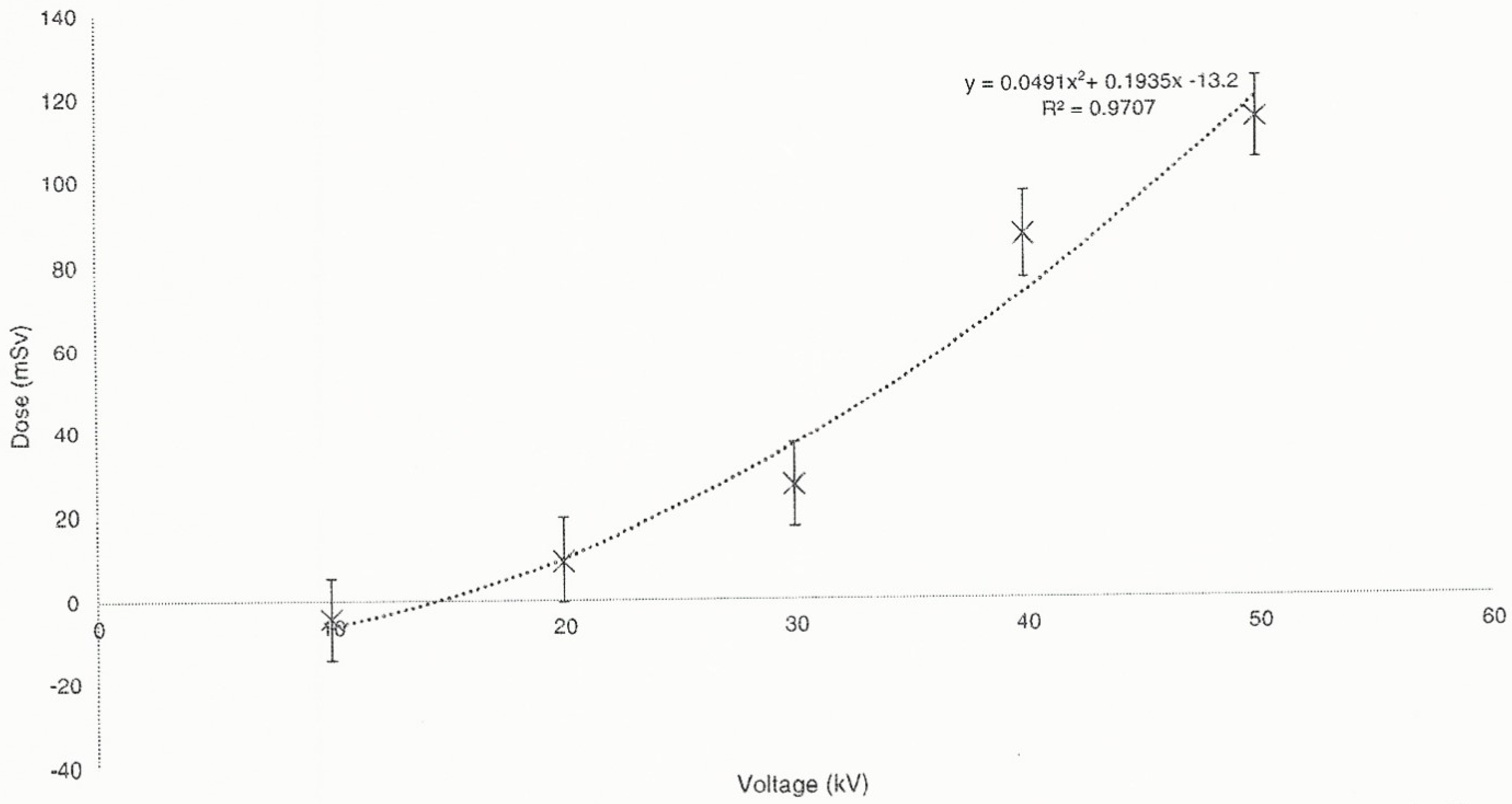

Fig. 2. Radiation entrance skin dose (0.2 cm^2) changes with different x-ray tube voltage settings using 40 μA and silver and iron filtration.

Figs. 2, 3, and 4 show the significant nonlinear relationship between dose and changes in voltage of the portable XRF device with constant 40 μA and iron and silver, molybdenum and iron, and aluminum and titanium filtration. Fig. 5 shows the linear relationship between measured dose and current keeping 40 kV and the iron and silver filtration constant. Finally, Fig. 6 shows the relationship between surface bone dose and skin thickness, which decreased slightly with increasing skin thickness. Increasing the skin thickness over the dosimeters, which would potentially increase scatter, did not increase the dose measured by the OSLD. The 1-cm^2 skin dose measurements using aluminum and titanium, molybdenum and iron, and iron and silver filtration at 50 kV, 40 μA, and 3 min were 224.7, 49.0, and 103.7 mSv, respectively.

Thermoluminescent dosimeter measurements

We took measurements using TLDs to look at the radiation dose for in vivo measurements of toenail and bone with two separate measurements for each. The results for these measurements are summarized in Table 1. The average result from a grid of 4 TLD chips (~0.8 cm^2 area) arranged over the irradiated area during a bone and toenail measurement changed the dose to 48.8 and 43.3 mSv, respectively. The differences in dose quantification are explained in the Discussion section.

Simulation dose measurements

We used the simulation to calculate the dose of the bone surface and skin, which would be the only components that would receive radiation dose from in vivo measurements using the portable XRF. Using this, we can then calculate total-body effective dose for our measurements. The results for the measurements of skin dose and total-body effective dose for bone and toenail measurements are shown in Table 2. The leg was 40 cm in length to capture all scatter, but for the skin dose only a 1-cm^2 voxel was used to determine skin dose. For total-body effective dose, we used energy deposition in skin and bone surface, which we averaged over the previously mentioned total-body skin and bone surface

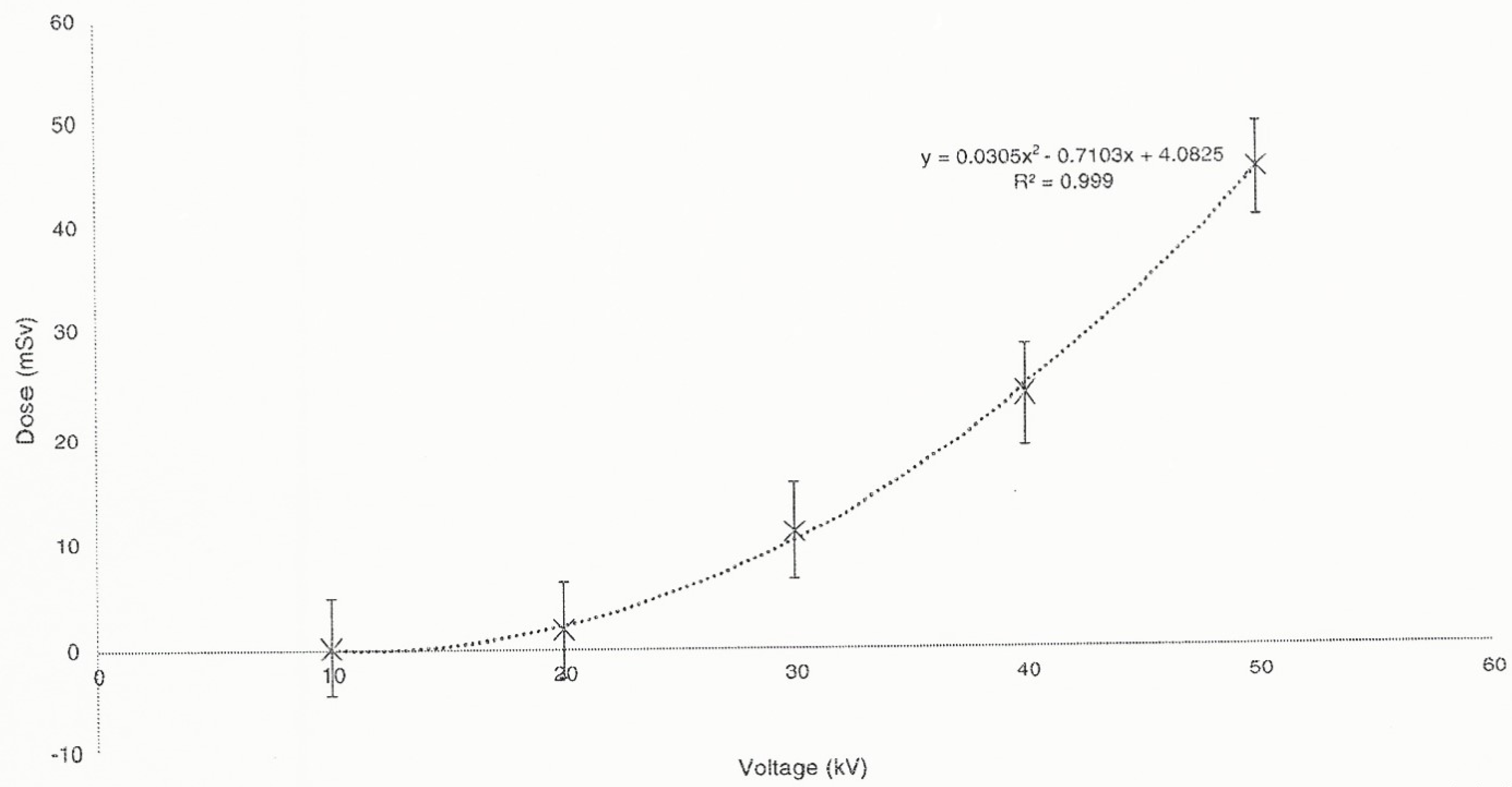

Fig. 3. Radiation entrance skin dose (0.2 cm^2) changes with different x-ray tube voltage settings using 40 μA and molybdenum and iron filtration.

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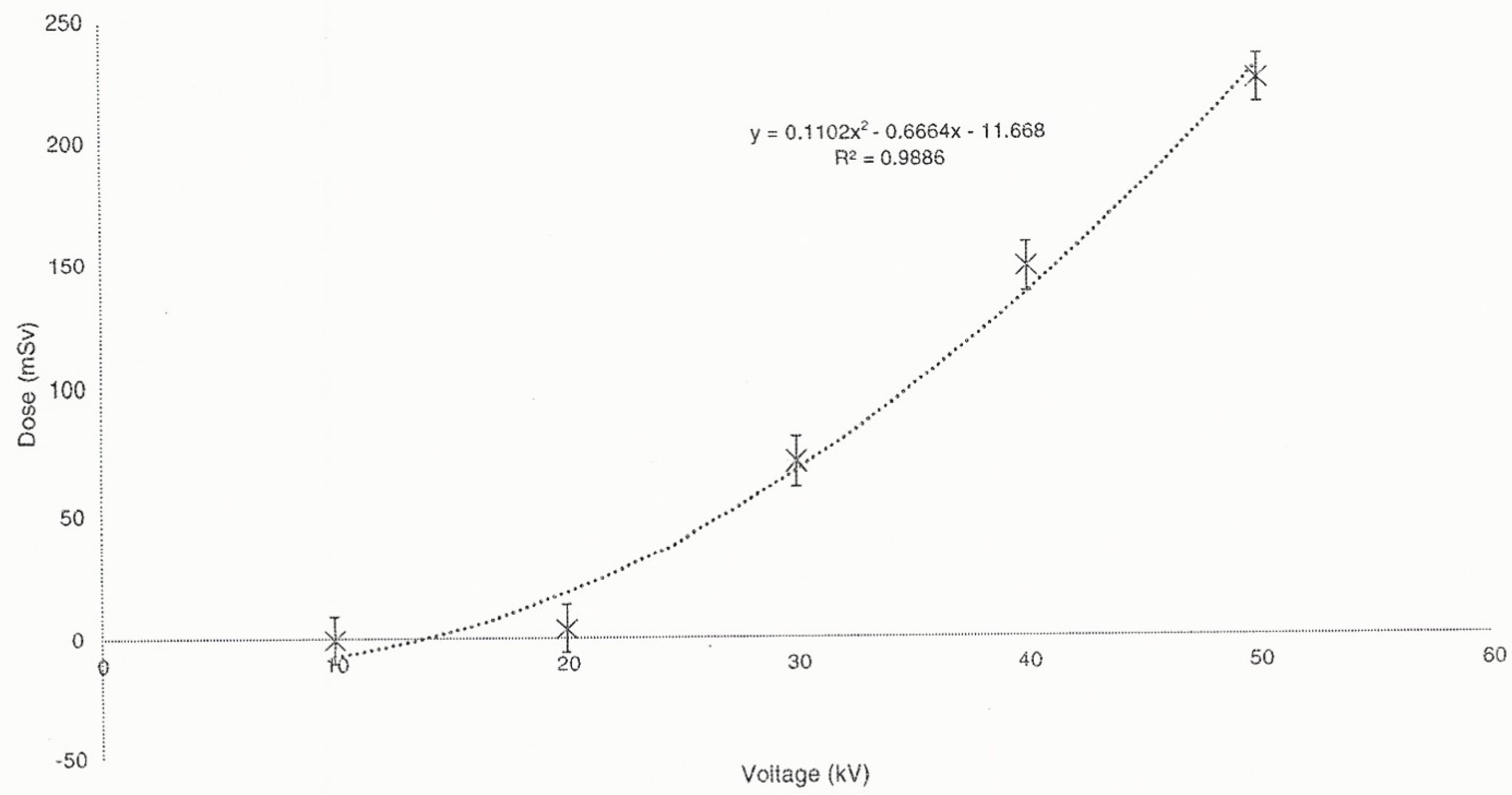

Fig. 4. Radiation entrance skin dose (0.2 cm^2) changes with different x-ray tube voltage settings using 40 μA and aluminum and titanium filtration.

areas to arrive at the final values. We assume all the dose going to the bone is surface dose, surface bone and skin are the only contributing factors to total-body effective dose in bone measurements, and the skin dose is the only contributing factor to total-body effective dose from the toenail measurements. We conservatively used female average values for 5-y-old, male for 10-y-old, and female for adult calculations to report the highest possible dose. The simulation resulted in a bone dose averaged over the simulated leg (40-cm long and 1.25-cm radius) of 2.2, 2.2, and 2.1 mSv for 5-y-old, 10-y-old, and adult, respectively. The simulated skin dose averaged over the total leg was 1.1 μSv. Changing the tissue thickness and bone surface dose resulted in a total-body effective dose of 3.4, 3.7, and 4.3 μSv at 5, 3, and 1 mm tissue thickness, respectively.

In vivo dose measurement comparisons

Table 3 shows a side-by-side comparison of the skin dose estimates made by measuring the dose with simulation, TLDs, and OSLDs, and their respective volume differences.

DISCUSSION

This study determined radiation doses from using portable XRF devices for in vivo measurements in order to determine the suitability for such use. We found the total-body effective dose delivered by the device in a 3-min measurement to be reasonable and skin dose to be at a level higher and more concentrated than typical of diagnostic exams but far from any deterministic radiation risk. We demonstrated the relationship of the radiation dose from the device with increasing time, amperage, and voltage in the x-ray tube, and the effect of different filtration on the radiation dose. Finally, we used simulations to determine and compare the experimental measures of skin and total-body effective dose measurements.

One limitation of our experimental results from the study is accounting for slight geometry changes in the measurements. The x-ray tube aperture is quite small, and for this reason, it was potentially easy to place a TLD or OSLD in a spot that did not reflect the highest potential dose. To combat this issue, we initially did measurements with

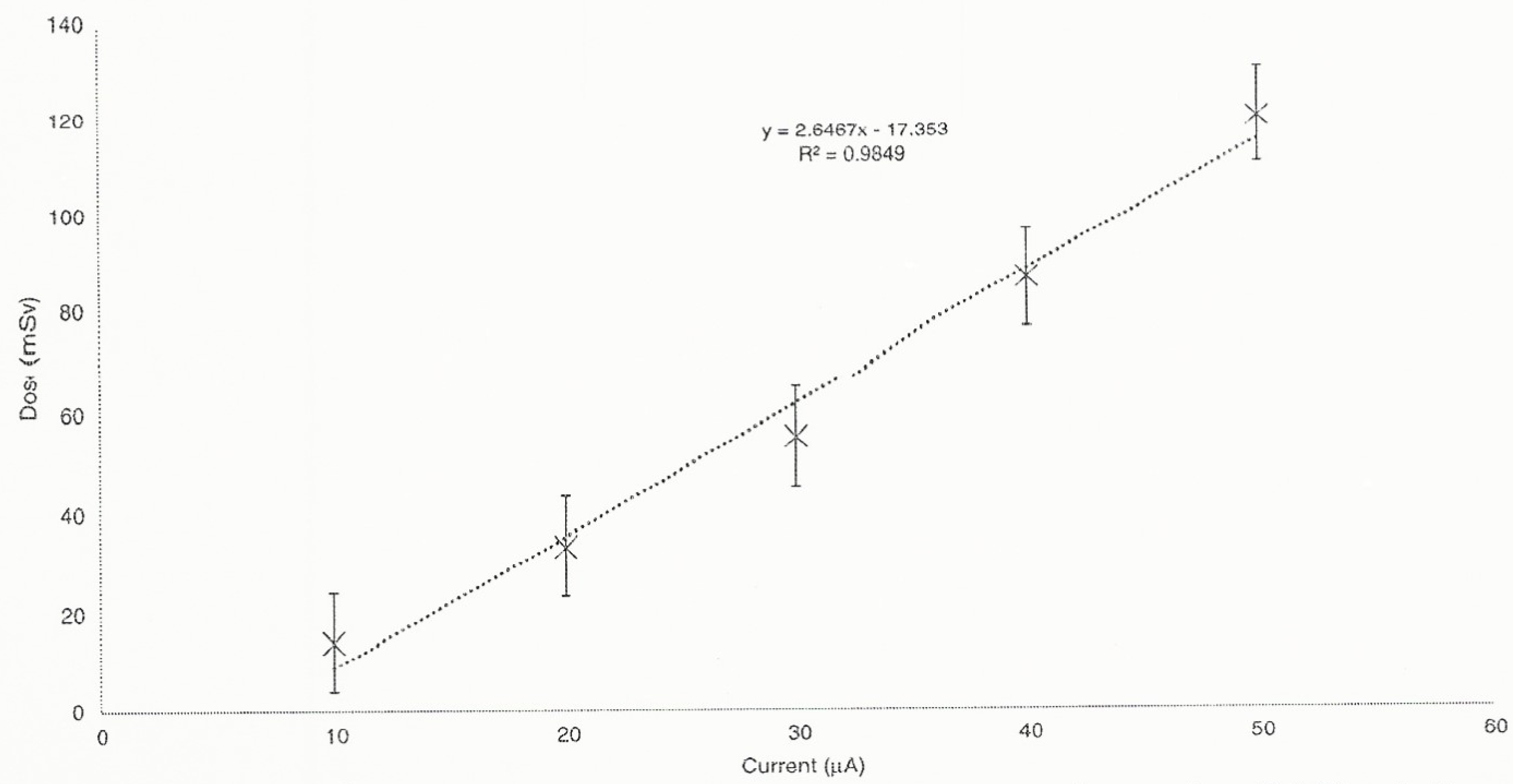

Fig. 5. Radiation entrance skin dose (0.2 cm^2) changes with different x-ray tube current settings using 40 kV and silver and iron filtration.

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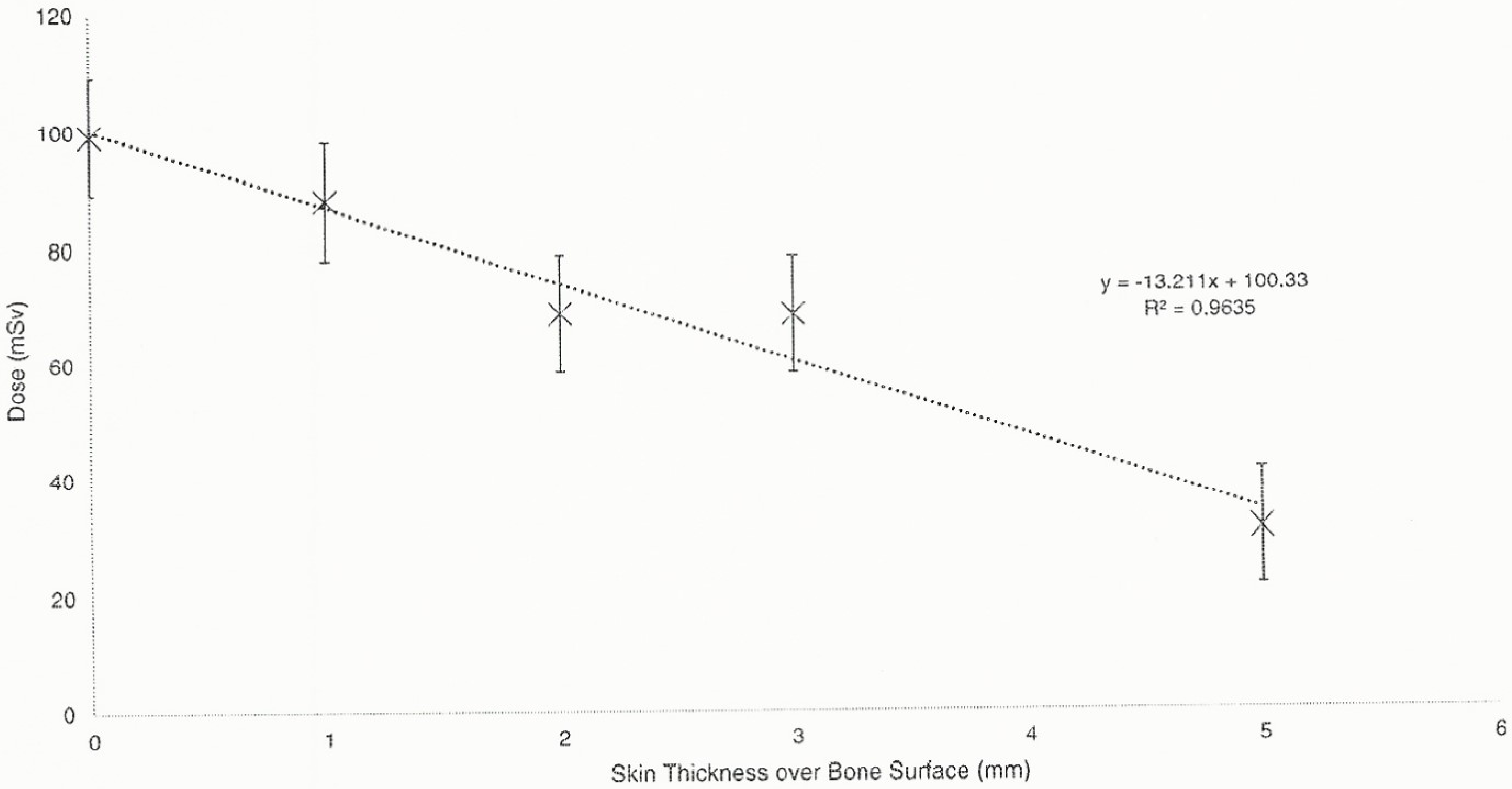

Fig. 6. Bone surface dose changes with increasing thickness of skin over bone using 50 kV, 40 μA, and silver and iron filtration.

multiple TLDs and OSLDs to determine the geometry with the maximal dose. This maximal dose geometry is what we attempted to replicate for the other measurements as part of the study. However, it is hard to determine whether or not the maximal dose was captured for every measurement, but the simulation results would not have had this same issue.

Using our phantom measurements, we were able to identify dose distribution changes with skin thickness. As expected, bone dose would decrease with increasing skin thickness over bone, but the results show a linear relationship. Over the small thickness increases shown with in vivo measurements of about 5 mm, the exponential interaction with attenuation is approximately the same as a linear relationship. Using National Institute of Standards and Technology (NIST) values for the attenuation coefficient of skin, we can determine what the approximate dose changes should be with increases in skin thickness assuming a perfectly collimated beam, and at 5 mm of skin thickness the bone surface dose should be 65.9 mSv. We show a value of 31.4 mSv for the bone surface dose at 5 mm of skin thickness. This difference is likely due to the x-ray tube source collimation being imperfect, and the beam likely spreads over a larger area with increasing distance, similar to an inverse square effect.

There was an observable difference in dose quantification between TLD, OSLD, and simulation measurements. This is mainly attributable to the varying averaged volumes for the doses for each of these measurements, which is evidenced by our results using a grid of four TLDs, which gave results in line with the estimated volume changes. In the singular TLD and OSLD measurements, we are not averaging over a true 1-cm^2 area but are measuring about 0.2 cm^2. Since the x-ray tube aperture of the portable XRF is actually smaller than 1 cm^2, it is likely most of the dose from entrance skin exposure to the x rays will be more concentrated than this initial area limit. Another potential reason for the quantification differences is in the calibration procedure for TLD and OSLD measurements. The calibration was done on standard TLD or OSLD chips, which were under almost uniform exposure. Since the dose from the portable XRF is highly concentrated at one area of the dosimeter, as mentioned above, it could affect the reading of the TLD and OSLD. In addition, the OSLDs were calibrated from standard OSLDs obtained from the manufacturer, but ideally they should be calibrated to include additional corrections due to fading, angular dependences, and beam quality that could all play a role in the differences identified between the results. However, the main use of the OSLDs in our study was to study the relationships of the radiation dose with changes in the in vivo measurement, which should be consistent regardless of quantification issues.

The phantoms used as a proxy for skin, bone, and toenails in our experimental setup were not able to perfectly represent the radiation interactions of real skin, bone, or toenails. Lucite as a skin phantom was shown to be spectrally equivalent to cadaver skin in a previous study, but even

Table 1. Skin dose to 0.2 cm^2 from in vivo measurements of bone and toenail.

Measurement	Dose measurements (mSv)	
	5-mm skin with bone	1.3-mm toenail
1	73.9	67.9
2	60.2	61.7

Table 2. Skin, bone, and total-body effective dose from bone and toenail portable XRF measurements.

	Total-body effective dose (μSv)	
	Bone measurement	Toenail measurement
5-y-old	7.4	4.4
10-y–old	4.9	2.9
Adult	3.4	2.0

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Table 3. Skin dose measurements from in vivo portable XRF measurements using different measurement techniques.

	Dose estimates (mSv)			
	TLD (0.2 cm^2)	TLD (~0.8 cm^2)	OSLD (0.2 cm^2)	Simulation (1 cm^2)
Bone measurement	73.9	48.8	103.7	48.5
Toenail measurement	67.9	43.3	111.7	28.7

considering this there are slight differences in attenuation and density. Similarly, the density and attenuation of plaster of paris is not the same as bone, as discussed in an in-depth calibration study (Da Silva and Pejovic-Milic 2017). The toenails were made to match attenuation coefficients of the characteristic x rays of specific metals of interest between 5–11 keV, as discussed in previous studies, but the attenuation coefficients will vary as the energy changes from the energies of interest which will also change the scattering dose (Roy et al. 2010; Zhang et al. 2017). These differences will likely reflect an increase in the radiation dose from scatter of around 10 to 20% for the phantom measurements in comparison to true in vivo measurements due to the increased scatter cross sections for the phantoms. Considering that the majority of the dose likely arises from direct interaction with the initial x-ray beam and the use of phantoms showed minimal increase in dose, we can accept these measurements and relationships to be slightly more conservative than true in vivo dose measurements. The simulation used accurately depicted human compositional and density data and included a life-size human leg for total-body effective dose quantification, so simulation results should be the most accurate in terms of comparisons to radiation dose experienced in a true in vivo measurement.

Using the total-body effective dose, we can estimate the risk of radiation-induced cancers. The increased risk for cancer and other inheritable effects from radiation has been found to be 5% per sievert of total-body effective dose (ICRP 2007). Given the doses we found from the 3-min portable XRF measurement, this would mean a 0.000004%, 0.000003%, and 0.000002% increased risk of cancer for 5-y-olds, 10-y-olds, and adults, respectively (ICRP 2007).

Deterministic effects from skin dose have been shown to occur for doses in excess of 2 Gy according to ICRP Publication 85; the portable XRF skin dose is 400 times less than this (ICRP 2000). This 2-Gy limit for skin doses is typically assigned assuming a uniform dose to an area; however, studies in radiation therapy patients have shown that when doses are limited to small areas, stem cells migrate from surrounding unaffected skin to repopulate the areas affected by DNA damage (von Essen 1969; Withers 1967). More recent studies have shown this to increase the resiliency of normal tissues by up to a factor of 4, which in the use of the portable XRF would further reduce the unlikely possibility of deterministic skin damage due to the small radiation beam used for measurements (Narayanasamy et al. 2017).

Given the minimal skin dose and total-body effective dose associated with these measurements, even measurement times as high as 10 min could be considered while maintaining a reasonable limit for exposure. The limit for total-body effective dose to any member of the public set by US Nuclear Regulatory Commission's (NRC) 10 CFR 20.1301 is at 1 mSv y^{-1} (US NRC 2018), which is 100–300 times more than given in a single 3-min measurement from our device.

The total-body effective dose measurements shown in Table 2 were taken as the highest dose considering differences in sex. We had sex-specific data only for total-body bone area and were not able to find sex-specific data for skin area. The dose difference between males and females was minor, with the greatest difference in the adult calculation of total-body effective dose of 2.9 μSv for males and 3.4 μSv for females. For 10-y-old males, doses were higher due to lower total bone area, since females typically have more growth earlier than males due to puberty. Almost all of the total-body effective dose arose from the absorbed dose in the surface of the bone.

The surface bone dose decreases slightly in relation to increases in the overlying tissue thickness, and detection accuracy for in vivo metal measurements decreases with increasing skin thickness. For in vivo measurement, typically there is a tradeoff between accuracy of the measurement and radiation dose (Specht et al. 2014). As the surface bone dose decreases, so does the signal that arises from the bone, which in turn increases the uncertainty of the metal quantification measurement. In our previous study, we found 3-min measurements with 50 kV and 40 μA would achieve reasonable detection limits for populations with skin thicknesses less than 5 mm (Specht et al. 2014). In further application of the device, we found this to be a less reasonable assumption for all populations (Specht et al. 2016). With the results shown here, it seems that longer measurement times of up to 10 min would be feasible while maintaining acceptable radiation dose limits. This would reduce the detection limit by a factor of the square root of the increase in time or current, which in this case would be a decrease of a factor 1.8.

However, we need to make sure the increased measurement times would not be overexposing those with low tissue thickness in order to capture a greater proportion of the population. Our results indicate that the dose change for individuals with lower soft tissue thicknesses is relatively minor with an increase of about 0.8 μSv total-body effective dose from 5-mm to 1-mm tissue thickness for a 3-min measurement. The detection limit change over this tissue thickness difference is much more drastic with a detection limit

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of 11.0 and 1.8 ppm for 5- and 1-mm tissue thickness, respectively (Specht et al. 2014). This demonstrates that the primary limiting factors of the detection limit of the measurement come from a combination of the absolute efficiency of the detector, which decreases with the inverse square law from increasing tissue thickness and the added attenuation from soft tissue thickness. The inverse square drop off with distance is a result of the characteristic x-ray production in the bone being isotropic, which will greatly decrease the efficiency of the detector with increasing distance from the characteristic x rays arising in the bone. The added attenuation is a larger factor for the outgoing x-ray signal, since the initial x-ray beam is of higher average energy than the characteristic x-ray signal. Thus, the x-ray signal would have a higher interaction cross section and probability of attenuation with increases in tissue thickness. Although our results indicate the radiation dose and total number of interactions creating signal in the bone will change, that relationship is almost linear over the range of tissue thicknesses in the general population and will have limited impact on increases in the detection limit in comparison to the changes induced by the inverse square effect and outgoing signal attenuation.

CONCLUSION

This study looked at the radiation dose administered while taking in vivo metal measurements with a standard 2-W silver x-ray tube. We showed normal linear relationships between measurement time, x-ray tube current, and radiation dose with the device, and we showed a second order polynomial relationship with increasing voltage and radiation dose. Dose was quantified using TLDs, OSLDs, and simulations, which gave similar dose estimations. Skin dose for a standard 50-kV, 40-μA measurement of bone and toenails in vivo was 48.5 and 28.7 mSv according to simulation results. Total-body effective dose was shown as 3.4 and 2.0 μSv for in vivo bone and toenail measurements for adults using the portable XRF device with a 3-min measurement.

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Exhibit B

INTERIM UPDATE

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 723 • October 2017

(Replaces Committee Opinion Number 656, February 2016)

Committee on Obstetric Practice

This document is endorsed by the American College of Radiology and the American Institute of Ultrasound in Medicine. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Member contributors included Joshua Copel, MD; Yasser El-Sayed, MD; R. Phillips Heine, MD; and Kurt R. Wharton, MD. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

INTERIM UPDATE: This Committee Opinion is updated as highlighted to reflect a limited, focused change in the language and supporting evidence regarding exposure to magnetic resonance imaging and gadolinium during pregnancy.

Guidelines for Diagnostic Imaging During Pregnancy and Lactation

ABSTRACT: Imaging studies are important adjuncts in the diagnostic evaluation of acute and chronic conditions. However, confusion about the safety of these modalities for pregnant and lactating women and their infants often results in unnecessary avoidance of useful diagnostic tests or the unnecessary interruption of breastfeeding. Ultrasonography and magnetic resonance imaging are not associated with risk and are the imaging techniques of choice for the pregnant patient, but they should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient. With few exceptions, radiation exposure through radiography, computed tomography scan, or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with fetal harm. If these techniques are necessary in addition to ultrasonography or magnetic resonance imaging or are more readily available for the diagnosis in question, they should not be withheld from a pregnant patient. Breastfeeding should not be interrupted after gadolinium administration.

Recommendations

The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice makes the following recommendations regarding diagnostic imaging procedures during pregnancy and lactation:

- Ultrasonography and magnetic resonance imaging (MRI) are not associated with risk and are the imaging techniques of choice for the pregnant patient, but they should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient.
- With few exceptions, radiation exposure through radiography, computed tomography (CT) scan, or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with fetal harm. If these techniques are necessary in addition to ultrasonography or MRI or are more readily available for the diagnosis in question, they should not be withheld from a pregnant patient.
- The use of gadolinium contrast with MRI should be limited; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome.
- Breastfeeding should not be interrupted after gadolinium administration.

Introduction

Imaging studies are important adjuncts in the diagnostic evaluation of acute and chronic conditions. The use of X-ray, ultrasonography, CT, nuclear medicine, and MRI has become so ingrained in the culture of medicine, and their applications are so diverse, that women with recognized or unrecognized pregnancy are likely to be evaluated with any one of these modalities (1). However, confusion about the safety of these modalities for pregnant and lactating women and their infants often results in unnecessary avoidance of useful diagnostic tests

or the unnecessary interruption of breastfeeding. This document reviews the available literature on diagnostic imaging in pregnancy and lactation. Obstetrician–gynecologists and other health care providers caring for pregnant and breastfeeding women in need of diagnostic imaging should weigh the risks of exposure to radiation and contrast agents with the risk of nondiagnosis and worsening of disease. Planning and coordination with a radiologist often is helpful in modifying technique so as to decrease total radiation dose when ionizing radiation studies are indicated (Table 1).

Ultrasonography

Ultrasound imaging should be performed efficiently and only when clinically indicated to minimize fetal exposure risk using the keeping acoustic output levels As Low As Reasonably Achievable (commonly known as ALARA) principle. Ultrasonography involves the use of sound waves and is not a form of ionizing radiation. There have been no reports of documented adverse fetal effects for diagnostic ultrasonography procedures, including duplex Doppler imaging. The U.S. Food and Drug Administration limits the spatial-peak temporal average intensity of ultrasound transducers to 720 mW/cm^2. At this intensity, the theoretical increase in temperature elevation for the fetus may be as high as 2°C (35.6°F) (2, 3). However, it is highly unlikely that any sustained temperature elevation will occur at any single fetal anatomic site (3). The risk of temperature elevation is lowest with B-mode imaging and is higher with color Doppler and spectral Doppler applications (4).

Ultrasound machines are configured differently for different indications. Those configured for use in obstetrics do not produce the higher temperatures delivered by machines using nonobstetric transducers and settings. Similarly, although color Doppler in particular has the highest potential to raise tissue temperature, when used appropriately for obstetric indications, it does not produce changes that would risk the health of the pregnancy. However, the potential for risk shows that ultrasonography should be used prudently and only when its use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient (5). When used in this manner and with machines that are configured correctly, ultrasonography does not pose a risk to the fetus or the pregnancy.

Magnetic Resonance Imaging

The principal advantage of MRI over ultrasonography and computed tomography is the ability to image deep soft tissue structures in a manner that is not operator dependent and does not use ionizing radiation. There are no precautions or contraindications specific to the pregnant woman. Magnetic resonance imaging is similar to ultrasonography in the diagnosis of appendicitis, but when MRI is readily available, it is preferred because of its lower rates of nonvisualization (6). Although there are theoretical concerns for the fetus, including teratogenesis, tissue heating, and acoustic damage, there exists no evidence of actual harm. With regard to teratogenesis, there are no published human studies documenting harm, and the preponderance of animal studies do not demonstrate risk (1). Tissue heating is proportional to the tissue's proximity to the scanner and, therefore, is negligible near the uterus (1, 7). Finally, available studies in humans have documented no acoustic injuries to fetuses during prenatal MRI (1). In considering available data and risk of teratogenicity, the American College of Radiology concludes that no special consideration is recommended for the first (versus any other) trimester in pregnancy (8).

Unlike CT, MRI adequately images most soft tissue structures without the use of contrast. However, there are diagnostic situations in which contrast enhancement is of benefit. Two types of MRI contrast are available: 1) gadolinium-based agents and 2) superparamagnetic iron oxide particles. Gadolinium-based agents are useful

Table 1. Some Measures of Ionizing Radiation ⇦

Measure	Definition	Legacy Unit	SI* Unit
Exposure	Number of ions produced by X-ray or gamma radiation per kilogram of air	Roentgen (R)	2.58×10^{-4} C/kg
Dose	Amount of energy deposited per kilogram of tissue	Rad (rad)†	Gray (Gy)† 1,000 mGy = 1 Gy 1 Gy = 100 rad
Relative effective dose	Amount of energy deposited per kilogram of tissue normalized for biological effectiveness	Roentgen equivalent man (rem)	sievert (Sv) 1,000 mSv = 1 Sv 1 Sv = 100 rem

*International System of Units (SI) – these are preferred.

†For diagnostic X-rays, 1 rad = 1 rem, 1 Gy = 1 Sv.

Modified from Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, et al. General considerations and maternal evaluation. In: Williams obstetrics. 24th ed. New York (NY): McGraw Hill Medical; 2014. p. 926–39.

in imaging of the nervous system because they cross the blood–brain barrier when this barrier has been disrupted, such as in the presence of a tumor, abscess, or demyelination (9). Although gadolinium-based contrast can help define tissue margins and invasion in the setting of placental implantation abnormalities, noncontrast MRI still can provide useful diagnostic information regarding placental implantation and is sufficient in most cases (7).

Even though it can increase the specificity of MRI, the use of gadolinium-based contrast enhancement during pregnancy is controversial. Uncertainty surrounds the risk of possible fetal effects because gadolinium is water soluble and can cross the placenta into the fetal circulation and amniotic fluid. Free gadolinium is toxic and, therefore, is only administered in a chelated (bound) form. In animal studies, gadolinium agents have been found to be teratogenic at high and repeated doses (1), presumably because this allows for gadolinium to dissociate from the chelation agent. In humans, the principal concern with gadolinium-based agents is that the duration of fetal exposure is not known because the contrast present in the amniotic fluid is swallowed by the fetus and reenters the fetal circulation. The longer gadolinium-based products remain in the amniotic fluid, the greater the potential for dissociation from the chelate and, thus, the risk of causing harm to the fetus (8). The only prospective study evaluating the effect of antepartum gadolinium administration reported no adverse perinatal or neonatal outcomes among 26 pregnant women who received gadolinium in the first trimester (10). More recently, a large retrospective study evaluated the long-term safety after exposure to MRI in the first trimester of pregnancy or to gadolinium at any time during pregnancy (11). This study interrogated a universal health care database in the province of Ontario, Canada to identify all births of more than 20 weeks of gestation, from 2003 to 2015. Comparing first-trimester MRI (n=1,737) to no MRI (n=1,418,451), there were 19 stillbirths or deaths versus 9,844 in the unexposed cohort (adjusted relative risk [RR], 1.68; 95% CI, 0.97–2.90). The risk also was not significantly higher for congenital anomalies, neoplasm, or vision or hearing loss. However, comparing gadolinium MRI (n=397) with no MRI (n=1,418,451), the outcome of any rheumatologic, inflammatory, or infiltrative skin condition occurred in 123 versus 384,180 births (adjusted hazard ratio, 1.36; 95% CI, 1.09–1.69). Stillbirths and neonatal deaths also occurred more frequently among 7 gadolinium MRI-exposed versus 9,844 MRI unexposed pregnancies (adjusted RR, 3.70; 95% CI, 1.55–8.85). Limitations of the study assessing the effect of gadolinium during pregnancy include using a control group who did not undergo MRI (rather than patients who underwent MRI without gadolinium) and the rarity of detecting rheumatologic, inflammatory, or infiltrative skin conditions (12). Given these findings, as well as ongoing theoretical concerns and animal data, gadolinium use should be limited to situations in which the benefits clearly outweigh the possible risks (8, 12).

To date, there have been no animal or human fetal studies to evaluate the safety of superparamagnetic iron oxide contrast, and there is no information on its use during pregnancy or lactation. Therefore, if contrast is to be used, gadolinium is recommended.

The water solubility of gadolinium-based agents limits their excretion into breast milk. Less than 0.04% of an intravascular dose of gadolinium contrast is excreted into the breast milk within the first 24 hours. Of this amount, the infant will absorb less than 1% from his or her gastrointestinal tract. Although theoretically any unchelated gadolinium excreted into breast milk could reach the infant, there have been no reports of harm. Therefore, breastfeeding should not be interrupted after gadolinium administration (13, 14).

Ionizing Radiation Including X-rays

Commonly used for the evaluation of significant medical problems or trauma, X-ray procedures are indicated during pregnancy or may occur inadvertently before the diagnosis of pregnancy. In addition, it is estimated that a fetus will be exposed to 1 mGy of background radiation during pregnancy (2). Various units used to measure X-ray radiation are summarized in Table 1.

Concerns about the use of X-ray procedures during pregnancy stem from the risks associated with fetal exposure to ionizing radiation. The risk to a fetus from ionizing radiation is dependent on the gestational age at the time of exposure and the dose of radiation (15). If extremely high-dose exposure (in excess of 1 Gy) occurs during early embryogenesis, it most likely will be lethal to the embryo (Table 2) (15, 16). However, these dose levels are not used in diagnostic imaging.

In humans, growth restriction, microcephaly, and intellectual disability are the most common adverse effects from high-dose radiation exposure (Table 2) (2, 17). With regard to intellectual disability, based on data from atomic bomb survivors, it appears that the risk of central nervous system effects is greatest with exposure at 8–15 weeks of gestation. It has been suggested that a minimal threshold for this adverse effect may be in the range of 60–310 mGy (2, 18); however, the lowest clinically documented dose to produce severe intellectual disability is 610 mGy (14, 19). Even multiple diagnostic X-ray procedures rarely result in ionizing radiation exposure to this degree. Fetal risk of anomalies, growth restriction, or abortion have not been reported with radiation exposure of less than 50 mGy, a level above the range of exposure for diagnostic procedures (20). In rare cases in which there are exposures above this level, patients should be counseled about associated concerns and individualized prenatal diagnostic imaging for structural anomalies and fetal growth restriction (Table 3) (16).

The risk of carcinogenesis as a result of in-utero exposure to ionizing radiation is unclear but is probably

Table 2. Effects of Gestational Age and Radiation Dose on Radiation-Induced Teratogenesis ⇦

Gestational Period	Effects	Estimated Threshold Dose*
Before implantation (0–2 weeks after fertilization)	Death of embryo or no consequence (all or none)	50–100 mGy
Organogenesis (2–8 weeks after fertilization)	Congenital anomalies (skeleton, eyes, genitals)	200 mGy
	Growth restriction	200–250 mGy
Fetal period	**Effects**	**Estimated Threshold Dose***
8–15 weeks	Severe intellectual disability (high risk)†	60–310 mGy
	Intellectual deficit	25 IQ-point loss per 1,000 mGy
	Microcephaly	200 mGy
16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy*

*Data based on results of animal studies, epidemiologic studies of survivors of the atomic bombings in Japan, and studies of groups exposed to radiation for medical reasons (eg, radiation therapy for carcinoma of the uterus).

†Because this is a period of rapid neuronal development and migration.

Modified from Patel SJ, Reede DL, Katz DS, Subramaniam R, Amorosa JK. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. Radiographics 2007;27:1705–22.

very small. A 10–20 mGy fetal exposure may increase the risk of leukemia by a factor of 1.5–2.0 over a background rate of approximately 1 in 3,000 (7, 20). Thus, pregnancy termination should not be recommended solely on the basis of exposure to diagnostic radiation. Should a pregnant woman undergo multiple imaging studies using ionizing radiation, it is prudent to consult with a radiation physicist to calculate the total dose received by the fetus. The Health Physics Society maintains a website with an ask-the-expert feature: www.hps.org/publicinformation/ate/cat4.html. There is no risk to lactation from external sources of ionizing radiation (diagnostic X-rays) (21).

Computed Tomography

Computed tomography is a specific use of ionizing radiation that plays an important diagnostic role in pregnancy, and its use increased by 25% per year from 1997 to 2006 (1). Use of CT and associated contrast material should not be withheld if clinically indicated, but a thorough discussion of risks and benefits should take place (8). In the evaluation for acute processes such as appendicitis or small-bowel obstruction, the maternal benefit from early and accurate diagnosis may outweigh the theoretical fetal risks. If accessible in a timely manner, MRI should be considered as a safer alternative to CT imaging during pregnancy in cases in which they are equivalent for the diagnosis in question. Radiation exposure from CT procedures varies depending on the number and spacing of adjacent image sections (Table 2). For example, CT pelvimetry exposure can be as high as 50 mGy but can be reduced to approximately 2.5 mGy (including fetal gonad exposure) by using a low-exposure technique that is adequate for diagnosis. In the case of suspected pulmonary embolism, CT evaluation of the chest results in a lower dose of fetal exposure to radiation compared with ventilation-perfusion scanning (2). With typical use, the radiation exposure to the fetus from spiral CT is comparable with conventional CT.

Oral contrast agents are not absorbed by the patient and do not cause real or theoretical harm. The use of intravenous contrast media aids in CT diagnosis by providing for enhancement of soft tissues and vascular structures. The contrast most commonly used for CT is iodinated media, which carries a low risk of adverse effects (eg, nausea, vomiting, flushing, pain at injection site) and anaphylactoid reactions (9). Although iodinated contrast media can cross the placenta and either enter the fetal circulation or pass directly into the amniotic fluid (22), animal studies have reported no teratogenic or mutagenic effects from its use (8, 22). Additionally, theoretical concerns about the potential adverse effects of free iodide on the fetal thyroid gland have not been borne out in human studies (17). Despite this lack of known harm, it generally is recommended that contrast only be used if absolutely required to obtain additional diagnostic information that will affect the care of the fetus or woman during the pregnancy.

Traditionally, lactating women who receive intravascular iodinated contrast have been advised to discontinue breastfeeding for 24 hours. However, because of its water solubility, less than 1% of iodinated contrast administered to a lactating woman is excreted into the breast milk, and less than 1% of this amount of contrast will be absorbed through the infant's gastrointestinal tract. Therefore, breastfeeding can be continued without interruption after the use of iodinated contrast (1, 9, 13, 16, 23).

Table 3. Fetal Radiation Doses Associated With Common Radiologic Examinations ⇦

Type of Examination	Fetal Dose* (mGy)
Very low-dose examinations (<0.1 mGy)	
Cervical spine radiography (anteroposterior and lateral views)	<0.001
Head or neck CT	0.001–0.01
Radiography of any extremity	<0.001
Mammography (two views)	0.001–0.01
Chest radiography (two views)	0.0005–0.01
Low- to moderate-dose examinations (0.1–10 mGy)	
Radiography	
Abdominal radiography	0.1–3.0
Lumbar spine radiography	1.0–10
Intravenous pyelography	5–10
Double-contrast barium enema	1.0–20
CT	
Chest CT or CT pulmonary angiography	0.01–0.66
Limited CT pelvimetry (single axial section through the femoral heads)	<1
Nuclear medicine	
Low-dose perfusion scintigraphy	0.1–0.5
Technetium-99m bone scintigraphy	4–5
Pulmonary digital subtraction angiography	0.5
Higher-dose examinations (10–50 mGy)	
Abdominal CT	1.3–35
Pelvic CT	10–50
^{18}F PET/CT whole-body scintigraphy	10–50

Abbreviations: CT, computed tomography; PET, positron emission tomography.

*Fetal exposure varies with gestational age, maternal body habitus, and exact acquisition parameters.

Note: Annual average background radiation = 1.1–2.5 mGy, ^{18}F = 2-[fluorine-18]fluoro-2-deoxy-D-glucose.

Modified from Tremblay E, Therasse E, Thomassin-Naggara I, Trop I. Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation. Radiographics 2012;32:897–911.

Nuclear Medicine Imaging

Nuclear studies such as pulmonary ventilation-perfusion, thyroid, bone, and renal scans are performed by "tagging" a chemical agent with a radioisotope. This type of imaging is used to determine physiologic organ function or dysfunction rather than to delineate anatomy. Hybrid systems, which combine the function of nuclear imaging devices with computed tomography, improve the quality of information acquired and can help to correct artifacts produced by nuclear medicine imaging alone (9).

In pregnancy, fetal exposure during nuclear medicine studies depends on the physical and biochemical properties of the radioisotope. Technetium 99m is one of the most commonly used isotopes and is used for brain, bone, renal, and cardiovascular scans. Its most common use in pregnancy is in ventilation-perfusion lung scanning for detection of pulmonary embolism. In general, these procedures result in an embryonic or fetal exposure of less than 5 mGy, which is considered a safe dose in pregnancy. The half-life of this radioisotope is 6 hours, and it is a pure gamma ray emitter, which minimizes the dose of radiation without compromising the image (9). All these facts support the safety of technetium 99m at 5 mGy when indicated during pregnancy.

Not all radioisotopes can be used safely during pregnancy. Radioactive iodine (iodine 131) readily crosses the placenta, has a half-life of 8 days, and can adversely affect the fetal thyroid, especially if used after 10–12 weeks of gestation (9). Whether for diagnostic or therapeutic treatment purposes, iodine 131 should not be used during pregnancy. If a diagnostic scan of the thyroid is essential, technetium 99m is the isotope of choice.

Radionuclide compounds are excreted into breast milk in varying concentrations and for varying periods of time. In addition, rates of excretion of the same compound can vary between patients. Because some specific nuclear materials excreted into breast milk can have deleterious effects, consultation with experts on breastfeeding and nuclear medicine are recommended when these compounds are used in lactating women.

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Guidelines for diagnostic imaging during pregnancy and lactation. Committee Opinion No. 723. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e210–6.

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Exhibit C

Boston Children's Hospital

Contact the Department of Radiology
617-919-7226

International
+1-617-355-5209

Fax
617-730-0857

Treatments

Navigation

Bone Scan

A bone scan is a non-invasive imaging technique that uses a radioactive substance to visualize the bones. It is different from an x-ray or CT scan in that it shows cell activity in the bones.

How Boston Children's Hospital approaches bone scans

The Nuclear Medicine and Molecular Imaging program at Boston Children's is committed to providing a safe, comfortable and child-friendly atmosphere with:

- specialized nuclear medicine physicians with expertise in interpreting bone scans in children of all ages
- certified nuclear medicine technologists with years of experience imaging children and teens
- Child Life specialists to help families prior to and during exams
- equipment adapted for pediatric use, which means age-appropriate care for children
- protocols that keep radiation exposure as low as reasonably achievable while assuring high image quality

Frequently Asked Questions

What is a bone scan?

- A bone scan is a non-invasive imaging technique that uses a radioactive substance to visualize the bones, showing cell activity in the bone.
- A radiopharmaceutical called Technetium-99m MDP is injected into your child's veins. Technetium-99m MDP has a tiny amount of radioactive molecules in it.
- Once the radioactive substance has travelled through the bloodstream and into your child's bones, a special camera, called a gamma camera, is used to take pictures.

When might a bone scan be needed?

A bone scan can help assess:

- back pain
- bone infection
- occult fracture(s)
- stress fractures and stress injuries
- unexplained bone pain
- cancer
- damage to the bones due to exercise or trauma
- mandibular hypertrophy/hyperplasia
- osteoid osteoma
- avascular necrosis

How should I prepare my child for a bone scan?

There is no special preparation needed for this test.

- It is helpful to give your child a simple explanation as to why a bone scan is needed and assure him or her that you will be with him or her for the entire time.

- You may want to bring your child's favorite book, toy or comforting object to use during waiting times or in the imaging room.
- We have various DVDs to choose from for your child to watch during the procedure or you can bring one from home.

Between the injection of the radiopharmaceutical and the scan, there is a three to four hour delay. In addition, the scan time is approximately one hour. Please schedule your day accordingly.

What should I expect when I bring my child to the hospital for a bone scan?

When you arrive, please go to the Nuclear Medicine check-in desk on the second floor of the main hospital. A clinical intake coordinator will check in your child and verify his or her registration information.

What happens during a bone scan?

A bone scan involves three steps: injection of the radiopharmaceutical, a waiting period and the bone scan.

Injection of the radiopharmaceutical:

- You will be greeted by one of our nuclear medicine technologists who will explain to you and your child what will happen during the study.
- A tiny amount of the radiopharmaceutical will be injected into one of your child's veins by a small needle.

Waiting period:

- You and your child will be free to leave the department and then return 3 to 4 hours later for the actual imaging. The technologist will give you an exact time to return for imaging.
- While waiting, your child can conduct normal activities, including eating and drinking.
- It is important for your child to try to drink extra fluids during the waiting time in order to promote bladder emptying at the time of imaging.

The bone scan:

- When you return, your child will be asked to void/empty her bladder.
- Your child may be asked to change into hospital pajamas and will need to remove jewelry and any metal objects that could interfere with the scan.
- Your child will lie on the table and a large camera will be positioned above and underneath him/her.
- The camera does not make any loud noises and may move slowly around your child's body as pictures are taken.
- Your child may be asked to move into different positions in order for the bones to be viewed from different angles.
- It is important that your child remains still during the imaging in order to obtain the best quality images possible. If he/she moves, the images won't be as clear and we'll need to redo the pictures.

The number of images obtained and the total imaging time will vary depending on the diagnosis under consideration, although the average imaging time is about one hour.

Will my child feel anything during a bone scan?

Your child may experience some discomfort associated with the insertion of the intravenous needle. The needle used for the procedure is small. Once the radiopharmaceutical is injected, the needle is withdrawn and a bandaid is placed over the site of the injection. Your child may be a little sore in the area where we give her the injection.

Although the camera used to take pictures may appear large and intimidating, it does not touch your child.

Is a bone scan safe?

We are committed to ensuring that your child receives the smallest radiation dose needed to obtain the desired result.

It is safe to be in the room with your child the entire time, even if you are pregnant or nursing.

- Nuclear medicine has been used on babies and children for more than 40 years with no known adverse effects from the low doses employed.
- The radiopharmaceutical contains a very tiny amount of radioactive molecules, but we believe that the benefit to your child's health outweighs potential radiation risk.
- The camera used to obtain the images does not produce any radiation.

What happens after the bone scan?

Once the bone scan is complete, the images will be evaluated for quality by a nuclear medicine physician. If the scan is adequate, your child will be free to leave and resume normal activity.

The small amount of the radioactive substance in your child's body will dissipate over the first 24 hours following the test and pass out of your child's body through urine or stool. Drinking plenty of water will help to flush the radioactive material from your child's body.

How do I learn the results of the bone scan?

The nuclear medicine physician will provide a report to the doctor who ordered your child's bone scan. Your child's doctor will then discuss the results with you.

Related Conditions and Treatments

Osteoid Osteoma

Osteochondroma (Exostosis)

Osteoblastoma

Non-Ossifying Fibroma

Chondromas

Rhabdomyosarcoma

Exhibit D

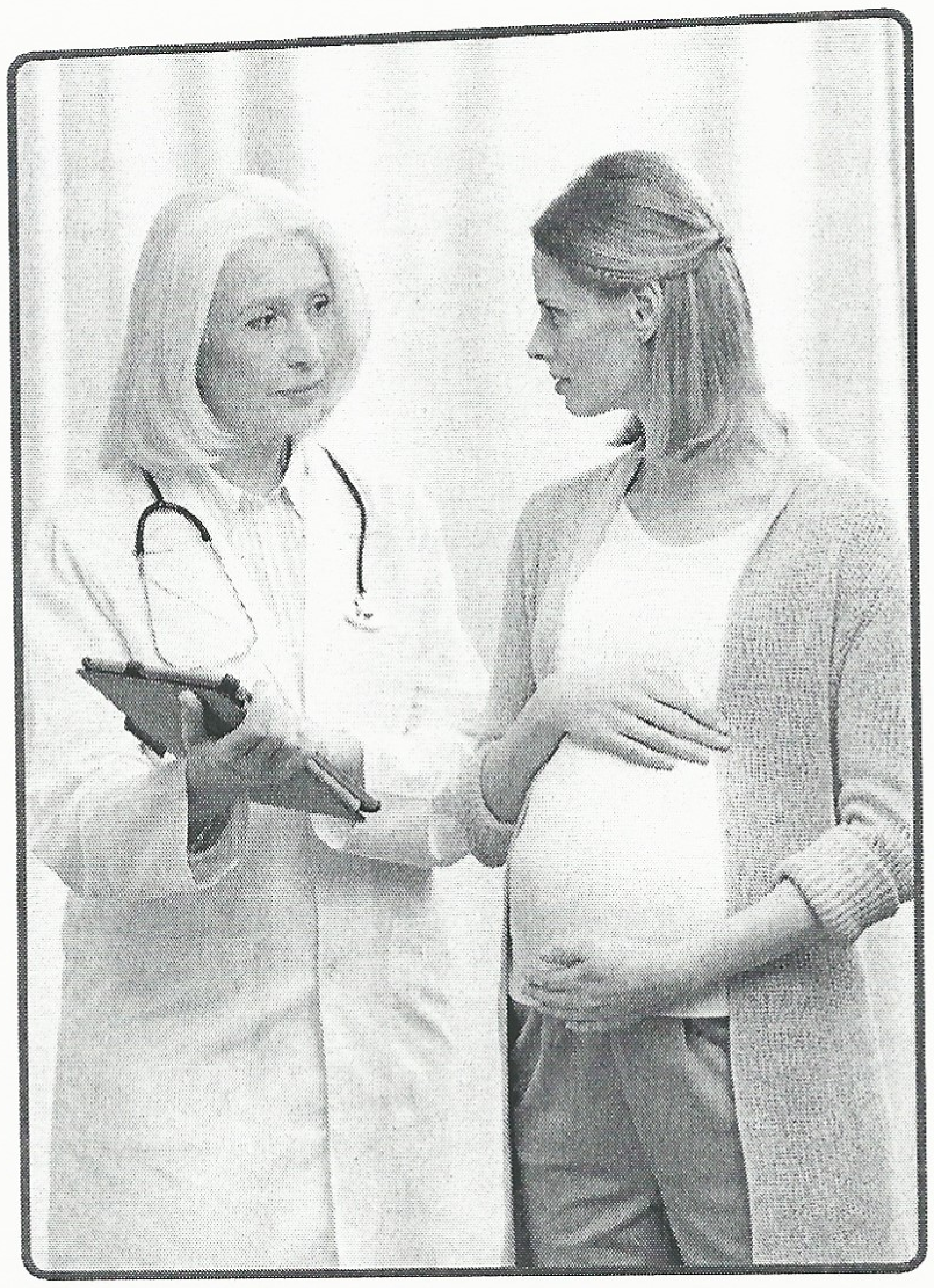
Radiation and Pregnancy:
Information for Clinicians

This overview provides physicians with information about prenatal radiation exposure as an aid in counseling pregnant women.

How to use this document

This information is for clinicians. If you are a patient, we strongly advise that you consult with your physician to interpret the information provided, as it may not apply to you. Information on radiation exposure during pregnancy for members of the public can be found on the Health Information for Specific Groups webpage (https://www.cdc.gov/nceh/radiation/emergency/prenatal.htm)

CDC recognizes that providing information and advice about radiation to expectant mothers falls into the broader context of preventive healthcare counseling during prenatal care. In this setting, the purpose of the communication is always to promote health and long-term quality of life for the mother and child.



Radiation exposure to a fetus

Most of the ways a pregnant woman may be exposed to radiation, such as from a diagnostic medical exam or an occupational exposure within regulatory limits, are not likely to cause health effects for a fetus.

However, accidental or intentional exposure above regulatory limits may be cause for concern.

Although radiation doses to a fetus tend to be lower than the dose to the mother, due to protection from the uterus and surrounding tissues, the human embryo and fetus are sensitive to ionizing radiation at doses greater than 0.1 gray (Gy). Depending on the stage of fetal development, the health consequences of exposure at doses greater than 0.5 Gy can be severe, even if such a dose is too low to cause an immediate effect for the mother. The health consequences can include growth restriction, malformations, impaired brain function, and cancer.

CDC ATSDR
National Center for Environmental Health
Agency for Toxic Substances and Disease Registry

CS303779-A April 29, 2019

Estimating the radiation dose to the embryo or fetus

Health effects to a fetus from radiation exposure depend largely on the radiation dose. Estimating the radiation dose to the fetus requires consideration of all sources external and internal to the mother's body, including the following:

- Dose from an external source of radiation to the mother's abdomen.
- Dose from inhaling or ingesting a radioactive substance that enters the bloodstream and that may through the placenta.
- Dose from radioactive substances that may concentrate in maternal tissues surrounding the uterus, such as the bladder, and that could irradiate the fetus.

Most radioactive substances that reach the mother's blood can be detected in the fetus' blood. The concentration of the substance depends on its specific properties and the stage of fetal development. A few substances needed for fetal growth and development (such as iodine) can concentrate more in the fetus than in corresponding maternal tissue.

Consideration of the dose to specific fetal organs is important for substances that can localize in specific organs and tissues in the fetus, such as iodine-131 or iodine-123 in the thyroid, iron-59 in the liver, gallium-67 in the spleen, and strontium-90 and yttrium-90 in the skeleton.

Radiation experts can assist in estimating the radiation dose to the embryo or fetus

Hospital medical physicists and health physicists are good resources for expertise in estimating the radiation dose to the fetus. In addition to the hospital or clinic's specialized staff, physicians may access resources from or contact the following organizations for assistance in estimating fetal radiation dose.

- The National Council on Radiation Protection and Measurements' Report No. 174, "Preconception and Prenatal Radiation Exposure: Health Effects and Protective Guidance" [NCRP2013] provides detailed information for assessing fetal doses from internal uptakes (https://ncrponline.org/).
- The International Commission on Radiological Protection's "Publication 84: Pregnancy and Medical Radiation" [ICRP2000] provides fetal dose estimations from medical exposures to pregnant women (http://www.icrp.org/publication.asp?id=ICRP%20Publication%2084).
- The Conference of Radiation Control Program Directors maintains a list of state Radiation Control/ Radiation Protection program contact information (https://www.crcpd.org).
- The Health Physics Society maintains a list of active certified Health Physicists (https://www.hps.org).
- The American Association of Physicists in Medicine provides information resources (https://www.aapm.org/org/positionstatements.asp).

Once the fetal radiation dose is estimated, potential health effects can be assessed.

Potential Health Effects of Prenatal Radiation Exposure (Other Than Cancer)

Table 1 summarizes the potential non-cancer health risks of concern. This table is intended to help physicians advise pregnant women who may have been exposed to radiation, not as a definitive recommendation. The indicated doses and times post-conception are approximations.

Table 1: Potential Health Effects (Other Than Cancer) of Prenatal Radiation Exposure

Acute Radiation Dose* to the Embryo/Fetus	**Time Post Conception** Up to 2 weeks	**Time Post Conception** 3rd to 5th weeks	**Time Post Conception** 6th to 13th weeks	**Time Post Conception** 14th to 23rd weeks	**Time Post Conception** 24th week to term
< 0.10 Gy (10 rads)†	Non-cancer health effects NOT detectable				
0.10–0.50 Gy (10–50 rads)	Failure to implant may increase slightly, but surviving embryos will probably have no significant (non-cancer) health effects.	Growth restriction possible	Growth restriction possible	Non-cancer health effects unlikely	
> 0.50 Gy (50 rads) The expectant mother may be experiencing acute radiation syndrome in this range, depending on her whole-body dose.	Failure to implant will likely be high, depending on dose, but surviving embryos will probably have no significant (non-cancer) health effects.	Probability of miscarriage may increase, depending on dose. Probability of major malformations, such as neurological and motor deficiencies, increases. Growth restriction is likely	Probability of miscarriage may increase, depending on dose. Growth restriction is likely.	Probability of miscarriage may increase, depending on dose. Growth restriction is possible, depending on dose. (Less likely than during the 6th to 13th weeks post conception) Probability of major malformations may increase	Miscarriage and neonatal death may occur, depending on dose.

8th to 25th Weeks Post Conception:

The most vulnerable period for intellectual disability is 8th to 15th weeks post conception
Severe intellectual disability is possible during this period at doses > 0.5 Gy
Prevalence of intellectual disability (IQ<70) is 40% after an exposure of 1 Gy from 8th to 15th week
Prevalence of intellectual disability (IQ<70) is 15% after an exposure of 1 Gy from 16th to 25th week

Note: This table is intended only as a guide. The indicated doses and times post conception are approximations.

* Acute dose: dose delivered in a short time (usually minutes). Fractionated or chronic doses: doses delivered over time. For fractionated or chronic doses, the health effects to the fetus may differ from what is depicted here.

† Both the gray (Gy) and the rad are units of absorbed dose and reflect the amount of energy deposited into a mass of tissue (1 Gy = 100 rads). In this document, the absorbed dose is that dose received by the entire fetus (whole-body fetal dose). The referenced absorbed dose levels in this document are assumed to be from beta, gamma, or x-radiation.

§ For adults, the LD50/60 (the dose necessary to kill 50% of the exposed population in 60 days) is about 3-5 Gy (300-500 rads) and the LD100 (the dose necessary to kill 100% of the exposed population) is around 10 Gy (1000 rads).

Table adapted from Table 1.1. of the National Council on Radiation Protection and Measurements' Report No. 174, "Preconception and Prenatal Radiation Exposure: Health Effects and Protective Guidance" [NCRP2013].

Gestational age and radiation dose are important determinants of potential non-cancer health effects. The following points are of particular note.

- During the first 2 weeks post-conception, the health effect of concern from an exposure of ≥ 0.1 Gy is the possibility of death of the embryo. Because the embryo is made up of only a few cells, damage to one cell, the progenitor of many other cells, may cause the death of the embryo, and the blastocyst may fail to implant in the uterus. Embryos that survive, however, are unlikely to exhibit congenital abnormalities or other non-cancer health effects, no matter what dose of radiation they received.
- In all stages post-conception, radiation-induced non-cancer health effects are not detectable for fetal doses below about 0.10 Gy.

Carcinogenic Effects of Prenatal Radiation Exposure

Radiation exposure to an embryo/fetus may increase the risk of cancer in the offspring, especially at radiation doses > 0.1 Gy, which are well above typical doses received in diagnostic radiology. However, attempting to quantify cancer risks from prenatal radiation exposure presents many challenges. These challenges include the following:

- The primary data for the risk of developing cancer from prenatal exposure to radiation come from the lifespan study of the Japanese atomic bomb (A-bomb) survivors. [Preston et al. 2008]. The analysis of that cohort includes cancer incidence data only up to the age of 50 years. This precludes making lifespan risk estimates as a result of prenatal radiation exposure.
- From the Japanese lifespan study [Preston et al. 2008], it can be concluded that for those exposed in early childhood (birth to age 5 years), the theoretical risk of an adult-onset cancer by age 50 is approximately ten-fold greater than the risk for those who received prenatal exposure. Therefore, the risk following prenatal exposure may be considerably lower than for radiation exposure in early childhood [NCRP2013].
- No reliable epidemiological data are available from studies to determine which stage of pregnancy is the most sensitive for radiation-induced cancer in the offspring [NCRP2013].

The lifespan study of the Japanese A-bomb survivors is continuing as the cohort ages. Future analyses of the accumulating data should provide a better understanding of the lifetime risk of cancer from prenatal and early childhood radiation exposure.

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For More Information on medical management and other topics on radiation emergencies:

Radiation Emergency Assistance Center/Training Site (REAC/TS) is a program uniquely qualified to teach medical personnel, health physicists, first responders and occupational health professionals about radiation emergency medical response. https://orise.orau.gov/reacts/

Radiation Emergency Medical Management (REMM) provides guidance to health care providers (primarily physicians) about clinical diagnosis and treatment of radiation injury during radiological and nuclear emergencies. https://www.remm.nlm.gov/

Conference of Radiation Control Program Directors https://www.crcpd.org

Health Physics Society https://www.hps.org

International Commission on Radiological Protection http://www.icrp.org/

National Council on Radiation Protection and Measurements https://ncrponline.org/

American Association of Physicists in Medicine https://www.aapm.org/org/positionstatements.asp